



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/615,497

07/07/2003

Doug Hui Huang

034827-1303

8961

30542

7590

11/24/2009

FOLEY & LARDNER LLP

P.O. BOX 80278

SAN DIEGO, CA 92138-0278

EXAMINER

JOHANNSEN, DIANA B

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

11/24/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/615,497	<b>Applicant(s)</b> HUANG, DOUG HUI	
	<b>Examiner</b> Diana B. Johannsen	<b>Art Unit</b> 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 July 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,4-18,30-32,46 and 49-52 is/are pending in the application.
- 4a) Of the above claim(s) 49 and 50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4-18,30-32,46,51 and 52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **FINAL ACTION**

1. This action is responsive to the Amendment and Reply filed July 10, 2009. Claims 1, 4, 6, 8, 12, and 30-31 have been amended, claims 36, 39-45, and 47-48 have been canceled, and claims 51-52 have been added. Claims 49-50 remain withdrawn (see also paragraph 3, below). Claims 1, 4-18, 30-32, 46, and 51-52 are now under consideration. Applicant's amendments and arguments have been thoroughly reviewed, but are moot in view of the new grounds of rejection set forth below, which new grounds were necessitated by applicant's claim amendments. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Election/Restrictions***

3. It is again noted that withdrawn claims 36, 39-45, and 47-48 have now been canceled. Applicant's prior election of the polymorphisms CYP2D6\*4, CYP2D6\*5, and CYP2D6\*Nx2 and of the primers of SEQ ID NOS 9, 14, and 11 in the reply of May 9, 2006 is again noted. Claims 49-50, as well as claims 9-10, 32 and 46 in part (to the extent drawn to non-elected species), remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. With regard to the separation of original species (a) and (b), election was made **without** traverse in the reply filed on November 24, 2008.

***Specification***

4. The substitute specification filed July 10, 2009 has been entered.
5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., pages 50, 54, and 57 of the specification). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. It is noted that this objection can be overcome by simply amending the specification to delete the recitation "http://" in each hyperlink.

***Comment regarding claim interpretation***

6. Applicant's comments regarding the terms "multiplex primers" and "multiplex" reaction/amplification are noted. Although these arguments are now moot in view of the amendment of the claims, for purposes of clarifying the record, it is noted that the examiner concurs that "multiplex" amplification or a "multiplex" reaction would properly be interpreted as a single reaction involving the amplification of multiple target sequences. However, applicant's claims as previously written required "using multiplex amplification primers comprising SEQ ID NOs: 1-4" in "amplifying" a target sequence (i.e., a requirement for a multiplex reaction/amplification was not actually indicated in the claims). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Applicant's specification includes no definition of the term "multiplex (amplification) primers," and states that the reactions of the invention "can be multiplexed" (see paragraph 85), suggesting that reactions may be performed in

Art Unit: 1634

either a multiplex or non-multiplex format. Claim terms must be given the broadest reasonable interpretation consistent with the specification (see MPEP 2111).

***Claim Rejections - 35 USC § 112, second paragraph***

7. Claims 1, 4-18, 30-32, 46 and 51-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-18, 30-32, 46 and 51-52 remain indefinite because it is unclear whether the claims are directed to methods of identifying “at least one” polymorphism or a single polymorphism, for the reasons given in the prior Office action of March 3, 2009.

**It is noted that applicant’s amendments have necessitated the inclusion of new dependent claims 51-52 in this rejection.** The reply argues that applicant’s amendments of dependent claims 8 and 12 to recite “at least one” moot the rejection. However, claim 1 itself remains internally inconsistent, as the preamble references “at least one” polymorphism while the body of the claim itself appears to be directed to a method in which only a single polymorphism is to be assayed. While applicant’s amendments do further clarify that the dependent claims further limit the “at least one ...polymorphism” of the preamble of claim 1, the actual methods steps of claim 1 appear to be directed to detection of only a single polymorphism. Thus, applicant’s amendments are not sufficient to overcome the present rejection.

Claim 18 remains indefinite because it is unclear how the claim further limits claim 1, for the reasons given in the prior Office action of March 3, 2009. The response traverses the rejection on the grounds that claim 18 “further limits claim 1 to the

Art Unit: 1634

instance where all polymorphisms are identified as absent” such that “claim 18 is a subset of the potential outcomes recited in claim 1”. These arguments have been thoroughly considered but are not persuasive. As noted above (and in the prior Office action), the body of the method of claim 1 appears to be directed to identification of the presence or absence of a single polymorphism. The claims as written do not appear to embrace a method such as that noted in applicant’s arguments, i.e., a method in which “all polymorphisms are identified as absent”. Further, the text of claim 18 never indicates where “wildtype P450 2D6” is to be detected; no mention is made of, e.g., the sample being assayed in claim 1, nor are any other elements referenced in claim 1 mentioned in claim 18. Accordingly, it remains unclear how claim 18 relates to the method being performed in claim 1.

**THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:**

Claim 52 is indefinite over the recitation of the limitation “wherein the extension primers differ in length”. This language does not specify with respect to what “the extension primers” differ, such that the manner in which claim 52 further limits the method of claim 1 is not made clear. For example, do the extension primers “differ in length” as compared to each other, as compared to the amplification primers of the claims, etc.? Further, to the extent that this language further limits the lengths of the extension primers as compared to one another, does the language require that each different extension primer employed have a unique length, or would, e.g., 2 different 15

Art Unit: 1634

nucleotide extension primers and 2 different 16 nucleotide extension primers be embraced by the claim? Clarification is required.

***Claim Rejections - 35 USC § 112, first paragraph***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY**

**APPLICANT'S AMENDMENTS:**

9. Claim 52 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

New claim 52 requires that "the extension primers differ in length". It is again noted that this language is indefinite for the reasons given above; thus, the actual structural requirements that applicant intends to impart via this claim language are not clear. Applicant points to paragraph 80 and Examples 3 and 4 as supporting this new claim limitation; however, while the cited examples recite particular groups of primers that are of different lengths, such particular examples do not equate with a general disclosure of the concept of extension primers that "differ in length" (particularly given that the meaning of this language is not clear). Paragraph 88 of the specification references the tagging of extension primers with "varying lengths of nonspecific

Art Unit: 1634

polynucleotides”; however, this limitation applies to tag lengths, not to overall primer lengths. Further, a review of the entire disclosure does not reveal any general disclosure of the concept of extension primers that “differ in length”. Thus, this claim amendment introduces new matter.

***Claim Rejections - 35 USC § 103***

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY  
APPLICANT'S AMENDMENTS:**

11. Claims 1, 4, 6-9, 11-18, 30-32, 46 and 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al (WO 02/38589 A2 [05/16/2002; filed 11/09/2001]) in view of Stuvén et al (Pharmacogenetics 6:417-421 [1996]; cite no. A69 of the IDS of 02/2004), Steen et al (Pharmacogenetics 5:215-223 [1995]), and Hersberger et al (Clinical Chemistry 46:8 (1072-1077 [2000]; cite no. A40 of the IDS of 02/2004), as evidenced by Goelet et al (WO 92/15712 [09/17/1992]).

The claims as amended are drawn to a method of “identifying the presence or absence of at least one cytochrome P450 2D6 polymorphism in a sample” comprising “(a) amplifying a cytochrome P450 2D6 gene sequence from the sample using amplification primers comprising SEQ ID NOs: 1-4 in a single reaction” and “(b) identifying the presence or absence of a cytochrome P450 2D6 polymorphism in the gene sequence amplified in (a) using a primer extension reaction comprising a plurality of extension primers and a set of distinctively labeled ddNTPs” (see text of independent claim 1).

It is noted that the portions of the Anastasio et al reference on which the instant rejection relies find support in provisional application 60/247,943, filed November 9, 2000.

Anastasio et al disclose methods of genotyping and haplotyping the CYP2D6 gene in which one or more of the polymorphisms present in the gene are detected (see entire reference). Anastasio et al disclose methods in which primer extension is employed to identify polymorphisms, and disclose “primer extension oligonucleotides” for use in their methods in which the 3' termini of the oligonucleotides are “complementary to the nucleotide located immediately adjacent to the polymorphism site” (see, e.g., pages 18 and 22-23, and claim 4). In these methods of Anastasio et al, isolated nucleic acids from an individual are amplified, and primer extension is performed on the amplified nucleic acids, wherein the identity of the terminator in the extended oligonucleotide is identified to determine the identity of the polymorphism(s) present (see, e.g., page 22 and claim 4). While Anastasio et al do not refer to the use

Art Unit: 1634

of “distinctively labeled ddNTPs” in their methods (as set forth in independent claim 1), Anastasio et al do disclose the use of the “polymerase-mediated primer extension method” of patent WO92/15712 (Goelet et al) in the identification of polymorphisms (page 23). Goelet et al teach that their method employs differently labeled terminators, such that the identification of the nucleotide at the position of interest may be established based on the identity of the detectable marker incorporated into the primer during extension (see entire reference, particularly pages 10-13 and 21-22, summarizing the primer extension method of Goelet et al). Thus, the Goelet et al reference provides extrinsic evidence that the primer extension method of Anastasio et al involves the use of “a set of distinctively labeled ddNTPs” as required by the claims.

It is further noted that Anastasio et al disclose the practice of primer extension assays on arrays in order to detect multiple polymorphisms “at the same time” (see page 19), as well as the use of sets of primer pairs to assay multiple polymorphic sites by primer extension (see page 22), and the investigation of “multiple polymorphic sites...simultaneously” (page 23). Further, Goelet et al disclose that primer extension involves the use of 4 differently labeled ddNTPs (see page 11), and also provide teachings of how primer extension may be performed to analyze “one or more specified positions” wherein “different positions can be determined simultaneously” (see, page 12, as well as pages 31-33). However, Anastasio et al as evidenced by Goelet et al do not teach amplifying “using amplification primers comprising SEQ ID NOs: 1-4 in a single reaction,” as required by the claims.

Like Anastasio et al, Stuvén et al teach methods for detecting multiple CYP2D6 gene polymorphisms/alleles (see entire reference). Stuvén et al disclose the use in their methods of a step of long distance PCR for amplification of the entire CYP2D6 gene, thereby providing a template usable in the simultaneous detection of multiple different polymorphisms (see entire reference, particularly the abstract and page 418). The primer pair employed in this long distance PCR is identical to the primer pair identified in the instant application as SEQ ID NOS 1-2 (see page 418, Table 1, the “preamplification” primers “P 1-5” and “n”). In view of the teachings of Stuvén et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Anastasio et al so as to have employed therein a step of preamplification with the primers of instant SEQ ID NOS 1 and 2. An ordinary artisan would have been motivated to have made such a modification because Stuvén et al specifically teach that such an amplification provides a convenient template for CYP2D6 genotyping, said template encompassing multiple polymorphisms that one analyzing the CYP2D6 genotyping would wish to detect.

Additionally, Stuvén et al further disclose that the null allele CYP2D6\*5 causes a poor metabolizer phenotype for CYP2D6 (see pages 417-418, left column), and suggest using the CYP2D6\*5 detection method of Steen et al in combination with methods directed at detecting other genotypes to obtain “comprehensive genotype” information (page 421, left column). A review of the Steen et al reference reveals that the method suggested by Stuvén et al is a PCR based detection method that employs primers identical to instant SEQ ID NOS 3-4 (see the entire Steen et al reference, particularly

Art Unit: 1634

the right column of page 217, the primers identified as “CYP-13” and “CYP-24”). While Stuvén et al teach separately performing the assay of Steen et al “in combination with” their newly developed assay to obtain “comprehensive genotype information” (see page 421, left column), the later published reference Hersberger et al teaches that long PCR amplification to detect the CYP2D6\*5 (deletion) allele may be combined with regular CYP2D6 gene amplification in a single tube assay (see entire reference, particularly the abstract, the Materials and Methods, Figure 5 and page 1076, right column). Thus, Hersberger et al establish that CYP2D6 gene amplification and detection of the deletion allele may successfully be performed simultaneously in a single reaction. Additionally, Hersberger et al teach that the simultaneous amplification of CYP2D6 and CYP2D6\*5 in a single assay provides a control “for the reliability of the PCR” and allows one to gain further genotype information in a single reaction than is possible when separately assaying for CYP2D6\*5 (page 1076, right column).

In view of the teachings of Stuvén et al, Steen et al, and Hersberger et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method suggested by Anastasio et al in view of Stuvén et al so as to have included the primers of SEQ ID NOS 3 and 4 in a single amplification reaction with SEQ ID NOS 1-2, and thereby to have performed a method meeting all the requirements of the claimed invention. An ordinary artisan would have been motivated to have simultaneously assayed for both the alleles of Stuvén et al and the CYP2D6\*5 deletion allele using SEQ ID NOS 3-4 because Stuvén et al specifically suggest performing a reaction to allow for identification of CYP2D6\*5 in

Art Unit: 1634

combination with their own assay to achieve “comprehensive” genotyping of CYP2D6, and further suggest the use of SEQ ID NOS 3-4 of Steen et al in doing so. With regard to the requirement that SEQ ID NOS 1-4 be employed “in a single reaction,” the teachings of Hersberger et al would have motivated one of ordinary skill in the art to have performed such an assay to achieve the advantages of providing a simultaneous control for PCR reliability and allowing one to gain further genotype information in a single reaction than is possible when separately assaying for CYP2D6\*5, as is taught by Hersberger et al.

Regarding dependent claim 4, it is noted that the method of Goelet et al (i.e., the method relied upon by the Anastasio et al reference) requires identification of the detectable marker present on the terminator incorporated during primer extension (see, e.g., pages 11 and 22), and Goelet et al teach subjecting labeled, extended primers to polyacrylamide gel electrophoresis (see, e.g., page 38 and 43), such that the technique employed by Anastasio et al encompasses electrophoresis of primer extension reaction products.

With respect to claim 6, Goelet et al also disclose automated methods (see, e.g., page 51-52).

Regarding claim 7, Goelet et al disclose the labeling of each terminator with a different fluorophore (see, e.g., page 20).

Regarding claims 8-9, 18, 32, and 46, Anastasio et al disclose more than 40 polymorphisms of the CYP2D6 gene, including multiple polymorphisms encompassed by the claims, and disclose detection of numerous haplotypes/genotypes of CYP2D6,

Art Unit: 1634

including the wild type gene (see entire reference). With regard to the polymorphisms elected by applicant, it is particularly noted that the polymorphism identified by Anastasio et al as "PS33" corresponds to CYP2D6\*4 (see, e.g., page 4 and Figure 1B). It is also again noted that Stuvén et al suggest detection of CYP2D6\*5 by the method of Steen et al.

Regarding claims 12-17, 30-32, and 46, Anastasio et al disclose that CYP2D6 is a "pharmaceutically-important" gene whose gene product is involved in metabolism of a variety of drugs including "antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants," and teach that CYP2D6 genotype affects the extent to which a variety of drugs are metabolized in subjects (see, e.g., pages 1-3). With further regard to claims 30-32 and 46, Anastasio et al also teach the use of their genotyping/haplotyping methods in selecting appropriate drugs for treatment of a disease or condition (see, e.g., pages 7, 26-27), and therefore the teachings of Anastasio et al in view of Stuvén et al and Steen et al suggest the methods of the claims.

Regarding claim 11, it is noted that the samples disclosed by Anastasio et al are human samples (see entire reference, particularly, e.g., the examples).

Regarding new claim 51, Anastasio et al teach that their assay may be conducted using primers that are "in solution"; see, e.g., pages 22-23, as well as, e.g., claims 4 and 8.

Regarding new claim 52, it is noted that the primer extension oligonucleotides exemplified by Anastasio et al at, e.g., page 18-19, differ in length with respect to SEQ

Art Unit: 1634

ID NOS 1-4, such that the present combination of references suggests the claimed invention.

12. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Stuvén et al, Steen et al, and Hersberger et al, as evidenced by Goelet et al, as applied to claims 1, 4, 6-9, 11-18, 30-32, 46 and 51-52, above, and further in view of Dovichi and Zhang (Methods in Molecular Biology 167:225-239 [2001]; cite no. A20 of the IDS of 02/2004).

It is again noted that the combined references of Anastasio et al, Stuvén et al, Steen et al, and Hersberger et al, as evidenced by Goelet et al, teach identification of the terminator incorporated during primer extension by polyacrylamide gel electrophoresis of a labeled primer extension products. However, these references do not teach the use of capillary electrophoresis, as required by claim 5.

Dovichi and Zhang teach that capillary electrophoresis (CE) allows for the more rapid determination of a DNA sequence as compared to conventional polyacrylamide gel electrophoresis (PAGE)(see entire reference, particularly pages 227-228). In view of the teachings of Dovichi and Zhang, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Anastasio et al in view of Stuvén et al, Steen et al, and Hersberger et al, as evidenced by Goelet et al, so as to have subjected extended primers to CE rather than PAGE. An ordinary artisan would have been motivated to have made such a modification for the advantage of more rapidly determining the terminal base present in extended primers, as suggested by the teachings of Dovichi and Zhang.

Art Unit: 1634

13. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anastasio et al in view of Stuvén et al, Steen et al, and Hersberger et al, as evidenced by Goelet et al, as applied to claims 1, 4, 6-9, 11-18, 30-32, 46, and 51-52, above, and further in view of Pastinen et al (PCR Applications (1999), pages 521-535; Innis, M.A. et al, editors, Academic Press, San Diego).

Anastasio et al, Stuvén et al, Steen et al, and Hersberger et al, as evidenced by Goelet et al, do not teach an extension primer having any of SEQ ID Nos 9-19, as required by the claim. It is again noted that Applicant has elected SEQ ID Nos 9, 11, and 14 for examination.

Pastinen et al disclose a method of genotyping the CYP2D6 gene that accomplishes detection of multiple CYP2D6 alleles, including the elected CYP2D6\*4 allele, by primer extension (see entire reference, particularly pages 529-530). The primer employed by Pastinen et al in detection of the CYP2D6\*4 allele, primer 2D6\*4 (see page 530), comprises the sequence identified by applicant as SEQ ID NO: 9.

In view of the teachings of Pastinen et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method suggested by Anastasio et al in view of Stuvén et al, Steen et al, and Hersberger et al, as evidenced by Goelet et al, so as to have employed therein the 2D6\*4 primer of Pastinen in the detection of the CYP2D6\*4 allele of the CYP2D6 gene. As Anastasio et al, Stuvén et al, Steen et al and/or Hersberger et al do not exemplify detection of this allele using primer extension, and as Pastinen et al exemplify the successful use of their primer in detection of the CYP2D6\*4 allele, an ordinary artisan

Art Unit: 1634

would have been motivated to have made such a modification (as opposed to, e.g., experimenting with various primers in order to identify an appropriate primer) for the advantage of more rapidly and conveniently achieving detection of the CYP2D6\*4 allele.

### ***Response to arguments***

14. Applicant's arguments regarding the prior rejections of the claims under 35 USC 103 have been fully considered; however, these arguments are moot in view of the new grounds of rejection set forth herein. Particularly, applicant's amendment of independent claim 1 to require the use of SEQ ID NOS 1-4 "in a single reaction" necessitated new grounds of rejection in which the Hersberger et al reference is relied upon. It is acknowledged that Stuvén et al do teach detection of the CYP2D6\*5 allele via the "separate PCR assay" of Steen et al. However, Stuvén et al make clear that Steen et al's assay was "recently described" – i.e., a new assay – at the time they developed their own assay (page 421, left column). In a reference published a few years later (but still prior to applicant's effective filing date), Hersberger et al (2000) make clear that CYP2D6 and CYP2D6\*5 may successfully be amplified together in a single reaction, and disclose advantages of doing so, as indicated in the rejection now of record. Thus, at the time applicant's invention was made (which is the appropriate date for evaluating obviousness of the invention), the claimed invention would have been obvious to one of ordinary skill in the art.

### ***Conclusion***

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

Art Unit: 1634

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1634

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/  
Primary Examiner, Art Unit 1634